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CERTIFICATE

This certificate is issued in support of an application for Patent registration in a country outside New Zealand pursuant to the Patents Act 1953 and the Regulations thereunder.

I hereby certify that the annexed is a true copy of the Provisional Specification as filed on 3 September 1998 with an application for Letters Patent number 331719 made by Arjan Scheepens, Chris Edward Williams, Peter David Gluckman, Ross Graham Clarke.

Dated 30 September 1999.

Neville Harris
Commissioner of Patents

351719

Patents Form No. 4

PATENTS ACT 1953

PROVISIONAL SPECIFICATION

NEUROPROTECTION

We, **ARJAN SCHEEPENS**, a Netherlands citizen of 95 Elmore Road, RD3, Albany, Auckland, New Zealand; **CHRIS EDWARD WILLIAMS**, a New Zealand citizen of 2/73B Carlton Gore Road, Grafton, Auckland, New Zealand; **PETER DAVID GLUCKMAN**, a New Zealand citizen of 69 Park Road, Grafton, Auckland 1001, New Zealand; and **ROSS GRAHAM CLARK**, a New Zealand citizen of 25 Glen Road, Devenport, Auckland, New Zealand, do hereby declare this invention to be described in the following statement:

(followed by page 1A)

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NEUROPROTECTION

This invention relates to neuroprotection. In particular, it relates to a new therapeutic use of growth hormone and its analogs in neuroprotection.

BACKGROUND

The presence of growth hormone receptor/binding protein (GHR/BP) has been reported in both the juvenile[7] and adult[5] rat brains, and its pattern of distribution appears to be widespread, especially in the juvenile CNS. The ontogeny of expression of the GHR/BP also appears to be similar to IGF-1 and the IGF-1 receptor (IGF=1R) expression in the developing CNS, being produced mainly in fetal and early post-natal life and declining thereafter[2,4,6]. Studies of transgenic mice have showed that both IGF-1 knockout and GH deficient mice exhibit hypomyelinated, microcephalic brains[3,8], thus indicating a role for both GH and IGF-1 in brain growth, development and myelination. A recent study in GH-deficient children has shown a striking correlation between hypothalamic disturbances influencing GH secretion and their relative score in a visual motor psychological test, indicating a link between an abnormal somatotropic axis and reduced cognitive performance[1].

There has however to date been no suggestion that GH is neuroprotective. By "neuroprotective" is meant exhibiting both neuroprophylactic and neuronal rescue capabilities.

As used herein neuronal "rescue" is distinct from "prophylaxis". A neuronal "rescue" agent is one which, when administered after an insult prevents neurons from dying which would otherwise be destined to die. In contrast, a neuro-prophylactic agent is one which protects neurons against insult but only where the agent is present at the time of or before the insult.

It is the applicant's surprising finding that growth hormone is neuroprotective which underlies the present invention.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a method for inducing a neuroprotective effect in the brain of a patient which comprises the step of administering growth hormone, an analog thereof or a functionally equivalent ligand directly to the brain of said patient.

As used herein, "analog" means a fragment or variant of an active agent which has at least substantially equivalent biological activity to that active agent.

The term "functionally equivalent ligand" means an agent which binds to and activates the neural receptors in the brain which growth hormone binds to and

In a further aspect, the invention provides a method for inducing a neuroprotective effect in the brain of a patient which comprises the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the brain of said patient.

Preferably, the effective concentration of said growth hormone/analog/ligand is increased through direct administration.

Alternatively, the effective concentration of growth hormone or ligand is increased through administration of an agent which either stimulates production of growth hormone or the ligand or which lessens or prevents inhibition of growth hormone\ligand activity.

Preferably, the neuroprotective effect is a neural rescue effect.

Alternatively, the neuroprotective effect is a neuroprophylactic effect.

In a further embodiment, the invention provides a method of treating a patient to rescue neurons otherwise destined to die as the result of a prior neuronal insult which comprises the step of increasing the effective amount of growth hormone, an analog thereof or a functionally equivalent ligand in the brain of said patient.

As used herein, "neuronal insult" is used in its broadest possible sense and includes neuronal insults due to trauma (injuries), degenerative diseases and disorders, motor diseases and disorders, demyelinating diseases and disorders, neurological syndromes, eye diseases and sleep disorders.

The applicants have found that the neuroprotective role of growth hormone is mediated through the neural growth hormone receptors. By "neural growth hormone receptor" is meant any receptor found in the brain which growth hormone binds to and/or activates or to which growth hormone is capable of binding/activating. Such receptors include growth hormone receptor (GHR) and prolactin receptor (PRL-R).

Therefore, in a further aspect the invention provides a method for inducing a neuroprotective effect in the brain of a patient which comprises the step of causing an increase in the activity of neural growth hormone receptors in the brain of said patient.

Preferably, the increase in activity is the result of direct administration to the brain of said patient of an agent which increases the activity of said neural growth hormone receptors.

Preferably, said agent is one which binds growth hormone receptors directly. Such an agent can be growth hormone, an analog thereof or a functionally equivalent ligand such as prolactin, an analog of prolactin, placental lactogen or an analog of placental lactogen.

Alternatively, the agent is one which effects an increase in the active concentration of an agent which binds neural growth hormone receptors (ie. the agent administered acts indirectly). Preferably, such an agent is selected from growth hormone releasing proteins (GRP), growth hormone releasing hormone (GHRH), functionally equivalent secretagogues of these and somatostatin release inhibitory factor (SRIF).

Conveniently, the method is neuroprophylactic.

Alternatively, said method induces a neural rescue effect.

In still a further aspect, the invention provides a method of treating a patient to rescue neurons otherwise destined to die as the result of a prior neuronal insult which comprises the step of causing an increase in the activity of neural growth hormone receptors in the brain of said patient.

The applicants also contemplate a combination therapy in which growth hormone or an analog/ligand thereof can be administered to rescue a first population of neuronal cells and a second neuroprotective agent can be administered to protect a second population of neuronal cells. The invention therefore further provides a method of treating a patient to protect neurons which comprises administering growth hormone, an analog thereof or a functionally equivalent ligand in

Preferably, the additional neuroprotective agent is selected from IGF-1, GPE, activin, NGF, TGF-β growth hormone binding proteins, IGF-binding proteins and bFGF.

Conveniently, the method induces a neuronal rescue effect to rescue neurons otherwise destined to die as the result of neuronal insult.

In one embodiment, the insult is Huntington's disease or Alzheimer's disease and said growth hormone/analog/ligand is administered in combination with one or more of GPE, IGF-1 and activin.

In a further embodiment, the insult is corticobasal degeneration or Steele-Richardson-Olszewski syndrome and said growth hormone/analog/ligand is administered in combination with IGF-1.

In another embodiment, the insult is Devic's disease or Pick's disease and said growth hormone/analog/ligand is administered in combination with one or both of GPE and IGF-1.

In another embodiment, the insult is diabetic neuropathy and said growth hormone/analog/ligand is administered in combination with one or both of activin and IGF-1.

In still a further aspect, the invention provides a medicament for use in treating a patient to rescue neurons otherwise destined to die as the result of a prior neuronal insult which comprises, in combination, growth hormone, an analog thereof or a functionally equivalent ligand and one or more of GPE, activin, NGF, TGF-β, a growth hormone binding protein, an IGF binding protein and bFGF.

Preferably, said medicament further includes IGF-1.

In yet a further aspect, the invention provides the use of growth hormone or an analog thereof or a functionally equivalent ligand in the preparation of a neuroprotective medicament.

Preferably, said medicament is for use in rescuing neurons otherwise destined to die as the result of neuronal insult.

In a final aspect, the invention provides a method of identifying ligands suitable for use in rescuing neurons otherwise destined to die as a result of neuronal insult which comprises the step of screening candidate ligands for the ability to bind to and activate neural growth hormone receptors.

DESCRIPTION OF THE DRAWINGS

While the present invention is broadly defined above, those persons skilled in the art will appreciate that it is not limited thereto and that it further includes embodiments of which the following description provides examples. In addition, the invention will be better understood through reference to the accompanying drawings in which:

Figure 1 shows the effect of ICV rat growth hormone treatment on serum and CSF IGF-1 levels following moderate HI;

Figure 2 shows the effect of ICV rat growth hormone treatment on neuronal score following moderate HI; and

Figure 3 shows the effect of ICV rat growth hormone treatment on neuronal survival following moderate HI.

DESCRIPTION OF THE INVENTION

As broadly defined above, the present invention relates to neuroprotection. This is both in the sense of neuroprophylaxis and neuronal rescue, with the focus being on rescue.

The applicants have found that neuroprotection and in particular neuronal rescue is able to be effected using two approaches. The first approach is through a focus upon growth hormone, its analogs and functionally equivalent ligands. The applicants have found that increasing the effective concentration of growth hormone, its analogs or functionally equivalent ligands within the brain of a patient

The growth hormone which is used in this approach can be any mammalian growth hormone, with examples being human growth hormone, bovine growth hormone, rat growth hormone and porcine growth hormone. It is however preferred that the growth hormone employed be human growth hormone where the patient is a human.

The growth hormone which is used in this invention can be obtained from any commercial source.

Most conveniently, the effective concentration of growth hormone will be increased through direct administration using either growth hormone itself or a growth hormone pro-drug (a form which is cleaved within the body to release growth hormone). It is however not the applicants intention to exclude increasing growth hormone concentration through administration of either growth hormone agonists or secretagogues (substances which effect a direct increase in production of growth hormone within the brain (eg. growth hormone releasing peptides (GHRP) such as GHRP-1, GHRP-2, GHRP-6, Hexarelin, G-7039, G-7502, L-692,429, L-692,585, L-163,191, or growth hormone releasing hormone (GHRH)) or inhibitors of growth hormone antagonists (substances which bind growth hormone or otherwise prevent or reduce the action of growth hormone within the body). These latter compounds exert an indirect effect on effective growth hormone concentrations through the removal of an inhibitory mechanism, and includes substances such as somatostatin release inhibitory factor (SRIF).

Another possibility is administration of a replicable vehicle encoding growth hormone to the patient. Such a vehicle (which may be a modified cell line or virus which expresses growth hormone within the patient) could have application in increasing the concentration of growth hormone within the patient for a prolonged period. Such a vehicle could well form part of a brain implant.

In addition to growth hormone itself, the use of analogs of growth hormone or functionally equivalent ligands of growth hormone is contemplated.

As used herein, "analog" means a protein which is a variant of growth hormone through insertion, deletion or substitution of one or more amino acids but which retains at least substantial functional equivalency.

A protein is a functional equivalent of another protein for a specific function if the equivalent protein is immunologically cross-reactive with, and has at least substantially the same function as, the original protein. The equivalent can be, for example, a fragment of the protein, a fusion of the protein with another protein or carrier, or a fusion of a fragment with additional amino acids. For example, it is possible to substitute amino acids in a sequence with equivalent amino acids using conventional techniques. Groups of amino acids normally held to be equivalent are:

(a) Ala, Ser, Thr, Pro, Gly;
(b) Asn, Asp, Glu, Gln;
(c) His, Arg, Lys;
(d) Met, Leu, Ile, Val; and
(e) Phe, Tyr, Trp.

Functional equivalency of growth hormone analogs can also be readily screened for by reference to the ability of the analog to both bind to and activate the appropriate receptor. In this case, the receptor is a neural growth hormone receptor.

As indicated above, the term "neural growth hormone receptor" is used in this widest possible sense to cover all receptors on neuronal cell populations which growth hormone is capable of binding to and/or activating. Two such receptors are growth hormone receptor (GHR) and prolactin receptor (PRL-R). In particular, the term "neural growth hormone receptor" covers the human GHR and human PRL-R.

The human growth hormone receptor (GHR) is a 620 amino acid single chain protein containing a glycosylated 246 amino acid extracellular ligand binding domain, a single 24 amino acid transmembrane domain and a 350 amino acid cytoplasmic domain. The GHR monomer binds to a single growth hormone (GH) by binding site 1, a second GHR is then required to bind to binding site 2 on the same GH after which the receptor dimerises and signal transduction occurs. Signal transduction involves the activation of cytoplasmic kinases resulting in the phosphorylation of numerous cytoplasmic peptides.

The human prolactin receptor (PRL-R) is a 590 amino acid single chain polypeptide with a glycosylated 210 amino acid extracellular ligand binding domain, a single 24

The PRL-R monomer binds to a single prolactin (PRL). A second PRL-R is then required to bind to the same PRL after which the receptor dimerises and signal transduction occurs. Signal transduction involves the activation of cytoplasmic kinases resulting in the phosphorylation of numerous cytoplasmic peptides in a mechanism very similar to the GHR.

A second short form of the PRL-R has also been characterised. This receptor is the same as the long version of the receptor in the extracellular and transmembrane regions but has much smaller cytoplasmic domain of only 57 amino acids.

This leads to the applicants second approach to neuroprotection and in particular neuronal rescue. This approach focuses upon neural growth hormone receptors as defined above and upon effecting neuroprotection through the use of agents which both bind to and activate these receptors.

It will be appreciated that growth hormone and its analogs are agents which achieve this. Indeed, the use of growth hormone and growth hormone analogs represents a preferred aspect of the invention. However, it should be appreciated that this approach is not restricted to the use of growth hormone and its analogs but also extends to any ligand which fulfils the functional requirement of both binding to and activating (stimulating) the neural growth hormone receptors. Implicit in this will be the ability of the ligand to effect the initiation of intracellular signalling.

Examples of such ligands are prolactin and analogs of prolactin and placental lactogen and analogs of placental lactogen. These are also capable of binding to and activating neural growth hormone receptors.

Other stimulatory ligands can be identified by a screening protocol employing at least the ligand binding domain of a neural growth hormone receptor. This screening method can, for example, utilise the expression of the neural growth hormone receptor in Xenopus oocytes using standard recombinant DNA methods and measurement of the receptor-mediated signal transduction evoked by stimulatory ligands. Further classical "grind and bind" ligand-binding experiments can also be utilised. Here, whole brain or specific brain regions are homogenised and specific-binding of compounds to the neural growth hormone receptor characterised. This technique allows further characterisation of specificity and affinity (potency) of the compound for the receptor complex.

The methods of the invention are effectively therapeutic. For the intended therapeutic application, the active compound (growth hormone, analog or ligand) will be formulated as a medicament. The details of the formulation will ultimately depend upon the neuroprotective effect to be induced. Where the neuroprotective effect is a neuronal rescue effect, the formulation will be largely dependent upon the insult to be remedied and the route of administration but will usually include a combination of the active compound with a suitable carrier, vehicle or diluent.

To be effective as a neuroprotective agent, a variety of administration routes can be used. Examples include lumbar puncture, intracerebroventricularly (ICV), intraventricular administration involving neurosurgical insertion of a ventricular cannular with an abdominal pump and reservoir and intraparenchymal.

Dosage rates will also be formulation- and condition-dependent. However, by way of example, the recommended dosage rate of growth hormone formulated for injection would be in the range of 0.01 μg/100 g upwards.

The invention, in its various aspects, will now be illustrated by the experimental section which follows. It will however be appreciated that the experiments are non-limiting.

EXPERIMENTAL

Materials and Methods

Animal preparation

The following experimental procedures followed guidelines approved by the University of Auckland Animal Ethics Committee. Weaned 21 day old Wistar rats, weighing between 40 and 50g, were maintained on a 12 hour light and dark cycle and given free access to food and water throughout the study. The rats were paired by sex and weight and randomly assigned to either the treatment or control groups.

[redacted] described previously (Sirimanne *et al.*, J Neuroscience Methods, 55: 7-14, 1994). Briefly, the rats were anaesthetised and maintained on a 2% halothane/oxygen mixture and the right carotid artery ligated following exposure through a midventral neck incision. After surgery the rats were allowed to recover for 2 hours in a carefully controlled environment of 34°C with 85±5% relative humidity. They were then exposed to 15 minute hypoxia (8% oxygen in nitrogen).

Treatment

Commencing 2 hours after the end of hypoxia, rats in the treatment group (n=12) received 20μg recombinant rat growth hormone in a 10μl infusion, the control group received vehicle only. The infusion procedure was performed under heat lamps to prevent the animals from cooling. All solutions and needles were prepared and kept under aseptic conditions.

The rats were lightly anaesthetized again using 0.15ml Saffan™ (Pitman-Moore Ltd, NZ). The infusion was made into the right lateral cerebral ventricle guided by a metal cap fitted over the rat head using a modified technique originally described by Jirikowski (J Neuroscience Methods, 42: 115-118, 1992), in order to ensure correct placement of the infusion needle. Recombinant rat growth hormone (2mg/ml in 8.77mg/ml NaCl, 2.5mg/ml phenol, 2.0mg/ml polysorbate 20 and 10mM sodium citrate pH 6.0) or vehicle only was administered in a single dose at a rate of 1.0μl /minute controlled by a calibrated microinfusion pump. The infusion needles were left in place a further 3 minutes to prevent backflow.

CSF sampling

Three days after hypoxia cerebrospinal fluid (CSF) samples were taken. The rats were anaesthetised under Saffan anaesthesia and maintained on 2% halothane. They were then placed in a stereotaxic frame with the head flexed forward to allow blunt dissection of the muscle over the cisterna magna in order to expose the dura. A fine 30 gauge needle was then used to extract CSF with the aid of a binocular magnifier. The rats were euthanised by an overdose of sodium pentobarbitol administered ip and blood samples taken directly from the heart.

Histology

Brains were collected for histological processing after *in situ* fixation by transcardial perfusion with saline followed by a freshly prepared modified Bouin's solution (0.1M PBS, 4% paraformaldehyde [w/v], 0.08% glutaraldehyde [v/v], 15% picric acid [v/v of saturated solution]). Brains were removed, weighed and left in modified Bouin's solution overnight at room temperature. The following day the brains were placed in 70% ethanol for 3-4 days. The ethanol was replaced with fresh solution daily. The brains were then processed for paraffin embedding (dehydration through a graded series of ethanols, delipidation in chloroform, infiltration with paraffin wax, blocking in paraffin wax). Eight μm sections were cut from the tissue and placed on to poly-L-lysine pre-coated slides. Sections were stained using acid-fuschin/thionin.

Neuronal scoring procedure

Neural outcome was assessed using two levels in each brain; at the mid level of the striatum (Bregma + 0.8mm) and at the mid level of the dorsal horn of the hippocampus (Bregma –3.3). Neuronal outcome was assessed using two techniques:

1) Scoring in the cortex and hippocampus:

The frontoparietal cortex and the hippocampus were assessed by a blinded assessor for neuronal score using a standard five point neuronal loss score (Williams et al., Pediatric Research, 27: 561-565, 1990): 4= no damage, 3 = 0-10% cell loss, 2 = 11 to 50% cell loss, 1=51-90% cell loss, 0= >90% cell loss.

The cortex was scored at the level of the striatum (Bregma +8.0mm) and at the level of the dorsal horn of the hippocampus (Bregma –3.3) and was divided into 5 regions. The hippocampus was scored in the CA1/2, CA3 and dentate gyrus separately. The neuronal scores were then combined for each structure and compared between treatment groups.

2) Scoring in the striatum and thalamus:

Four regions each of the striatum and thalamus were scored using an ocular micrometer on a light microscope at 200x magnification. Each region was counted using 4 grids of the micrometer at 200μm^2/grid. Healthy neurons were counted in identical regions in the injured and contralateral hemisphere of each brain and % survival was calculated according to the following: counts RHS/counts LHS x 100 and compared between the treatment and control groups.

Radioimunoassay for IGF-1 in plasma and CSF

IGF-1 in blood plasma and CSF were measured using an IGF binding protein (IGFBP) blocked radioimunoassay (RIA) first described by Blum and Breier (Growth Regulation, 4: 11-19, [1994]). A polyclonal antibody (#878/4) raised in New Zealand white rabbits which has a very high affinity and specificity for IGF-1 and low cross-reactivity with IGF-II (0.01%) was used. This assay utilises a non-extraction process with samples diluted in acidic buffer and co-incubated with an excess of IGF-II. Dilution at pH 2.8 followed by addition of IGF-II serves to functionally block binding protein interference.

Plasma was diluted (1:200-1:400) in acidic buffer (20mM sodium phosphate pH 2.8, 0.1mM NaCl, 0.1% BSA, 0.02% NaN_3, 0.1% triton X-100) and CSF samples were diluted (1:11) in 0.5M sodium phosphate, 1% BSA, 1% triton X-100, 0.1% NaN_3, 1mM PMSF, pH 1.25 in order to dissociate IGFs from IGFBPs. The primary antibody, with IGF-II in excess at 25ng/tube, was diluted in a buffer that re-neutralised the pH (100mM sodium phosphate [pH7.8], 40mM NaCl, 0.02% NaN_3, 0.2% BSA, 0.1% triton X-100) to an initial working dilution of 1:50000). 0.1ml of diluted sample, control, or standard (rh-IGF-1, Genentech, San Fransisco) was incubated with 0.1ml of antibody-IGF-II solution and 0.1ml ^{125}I-IGF-1 at 15-20000 counts per tube. After incubation for 48 hours at 4°C, 1ml of the secondary

antibody complex was added and tubes incubated for a further 1 hour at room temperature. Following centrifugation at 3800rpm/30min at 4°C, tubes were decanted and the pellet counted by gamma counter.

Iodination of rh-IGF-I was performed using a modification of the Chloramine-T method of Hunter and Greenwood (Biochemical Journal, 91: 43-56, 1964). The validation of this assay system was performed according to the recommendations of the Third International Symposium on Insulin-Like Growth Factors (Bang *et al.*, Endocrinology, 136: 816-81, [1995]) including parallel displacement to the standard curve of CSF and recoveries of cold IGF-I. Recovery of unlabelled IGF-I in CSF was 89.6% (n=2). The ED-50 was 0.1ng/tube and the intra- and inter-assay coefficients of variation were 5% and 9% respectively.

Statistics

The data was analysed using paired t-tests or the non-parametric equivalent, Wilcoxon signed rank test. Calculations were performed using Sigmastat™ v2.0 (Jandel Scientific, San Rafael, California). All results are expressed as mean ± sem.

Results

The results are shown in Figures 1-3.

Growth hormone treatment had no effect on brain weight compared to vehicle only treated animals at post mortem (1.432±0.032 vs 1.455±0.028g).

Growth hormone treatment caused a trend towards a reduction in the fall in serum IGF-1 caused by the HI injury (159±7.3 vs135.8±11.7ng/ml, p=0.068). CSF IGF-1 levels were much lower than those in plasma. CSF IGF-1 levels were unchanged by the growth hormone treatment (3.82±0.35 vs 3.86±0.27ng/ml). This can be seen in Figure 1.

Cortical neuronal score was significantly improved by growth hormone treatment. The combined score for all five cortical regions at the levels of the striatum and hippocampus was (3.54±0.074 vs 2.98±0.124, p<0.001). This is shown in Figure 2.

Hippocampal neuronal score was significantly improved by growth hormone treatment. The combined score for CA1/2, CA3 and the dentate gyrus was (3.03± 0.176 vs 1.818±0.259, p=0.005). This is shown in Figure 2.

The neuronal survival score for the dorsolateral thalamus was significantly improved by growth hormone treatment. The combined score of the four areas counted and compared to the contralateral hemisphere was (104±2.18 vs 87.4± 4.67%, p=0.006). This is shown in Figure 3.

The neuronal survival score for the dorsolateral striatum was not significantly improved by the growth hormone treatment. The combined score of the four areas counted and compared to the contralateral hemisphere was (83.8±4.7 vs 75.3±6.1%,

Conclusions

Growth hormone administered centrally is effective as a neuronal rescue agent. The neuronal rescue effect occurred without a concurrent increase in CSF-IGF-1, suggesting the neuroprotective effect is independent of IGF-1.

Growth hormone was effective as a neuronal rescue agent in regions of the brain where the endogenous growth hormone receptor is expressed (cortex, hippocampus and thalamus) and not in areas where it is not (striatum). This suggests that the neuroprotective effect of GH is operating via either the growth hormone receptor or the prolactin receptor.

INDUSTRIAL APPLICATION

The invention therefore provides new approaches to neuroprotection. In particular, it provides new approaches to neuronal rescue.

The approaches of the invention have application in both therapy and prophylaxis. In particular, they have application in the treatment of patients who have suffered neuronal insult, including by injury, degenerative diseases and disorders, motor diseases and disorders, demyelinating diseases and disorders, neurological

syndromes, eye diseases and sleep disorders. Specifically contemplated are the following:

Injury

Stroke, traumatic brain injury, asphyxia, spinal injuries and CO toxicity.

Degenerative Diseases and Disorders

Familial and non-familial Alzheimer's disease, multi-infarct dementia, frontal lobe dementia of the non-Alzheimer-type, Pick's disease, Huntington's disease, Werdnig Hoffmann disease, Wernicke's encephalopathy, Ataxia-telangiectasia, Corticobasal degeneration, Down's syndrome, Rett syndome, IUGR, Alper's disease, Steele-Richardson-Olszewski syndrome, temporal lobe epilepsy, status epilepticus and undefined mental retardation.

Motor diseases and disorders

Spinocerebellar ataxia, progressive myoclonic ataxic syndrome, Leigh's disease, multiple system atrophy, the cerebral palsies, Friedeich's ataxia, pure hereditary spastic paraplegia, spinal muscular atrophies, diabetic neuropathy, hereditary sensory neuropathy type I, ALS, chronic idiopathic ataxic neuropathy, Tangier disease.

Demyelinating diseases and disorders

Inflammatory involvement: acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, Devic's disease, the leucodystrophies, Multiple Sclerosis; Non-inflammatory involvement: Progressive multifocal leucoencephalopathy, central pontine myelinolysis.

Neurological syndromes

Foetal alcohol syndrome, Autism and Myoclonic ataxia.

Eye diseases

Glaucoma

Sleep Disorders

Narcolepsy

Further, while the growth hormone/growth hormone receptor approach of the invention can be employed alone in the above therapies, it is also contemplated that a combination therapy approach can be taken. This latter approach involves administering, in particular, growth hormone or an analog\ligand thereof in combination with a second neuroprotective agent. This second neuroprotective agent will generally be protective, at least in part, of a population neuronal cells which is distinct from the population of neuronal cells which are protected by growth hormone and its analogs\ligands.

Such secondary neuroprotective agents include IGF-1, GPE, activin, NGF, TGF-β growth hormone binding protein, IGF-binding proteins (especially IGFBP-3), and bFGF.

Specific contemplated combinations are growth hormone and one or more of GPE, IGF-1 and activin for use in the therapy of Huntington's disease or Alzheimer's disease; growth hormone and IGF-1 for use in the therapy of corticobasal degeneration or Steele-Richardson-Olszewski syndrome; growth hormone and one or both of GPE and IGF-1 for use in the therapy of Devic's disease or Picks disease; and growth hormone and one or both of activin and IGF-1 for use in the therapy of diabetic neuropathy.

Where the combination therapy approach is viewed as desirable, the respective active agents can be formulated for co-administration, including as a single medicament. The invention therefore provides such neuroprotective medicaments which comprise, in combination, growth hormone or an analog thereof together with one or more of GPE, activin, NGF, TGF-β and bFGF. Where desirable, such medicaments can further include IGF-1.

Such medicaments can be prepared in any conventional manner, and can again include standard pharmaceutically-acceptable vehicles, carriers or diluents.

Those persons skilled in the art will appreciate that the above description is provided by way of example only and that the applicants are not limited in scope thereto.

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RUSSELL McVEAGH WEST WALKER

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FIGURE 1

Effect of ICV rat GH treament on serum and CSF IGF-1 levels following moderate HI

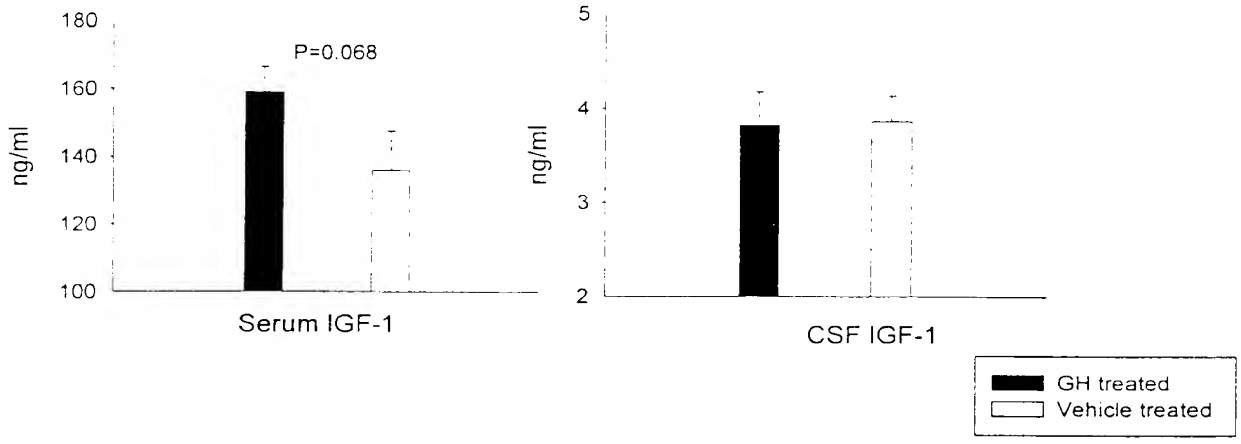

FIGURE 2

Effect of ICV rat GH treatment on neuronal score following moderate HI

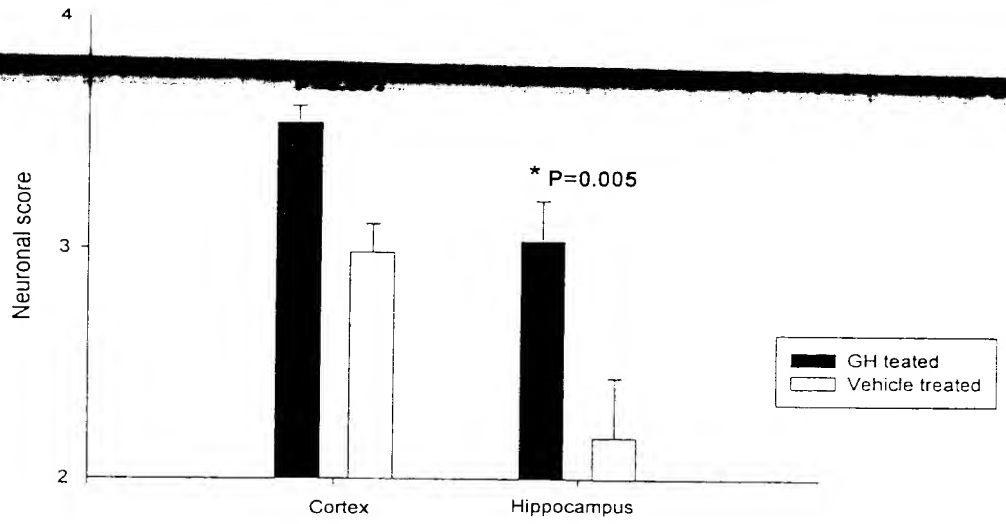

FIGURE 3

Effect of ICV rat GH treatment on neuronal survival following moderate HI